Cancer Mortality among Men Occupationally Exposed to Dichlorodiphenyltrichloroethane

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Abstract

Several studies have evaluated cancer risk associated with occupational and environmental exposure to dichlorodiphenyltrichloroethane (DDT). Results are mixed. To further inquire into human carcinogenicity of DDT, we conducted a mortality follow-up study of 4,552 male workers, exposed to DDT during antimalarial operations in Sardinia, Italy, conducted in 1946 to 1950. Detailed information on DDT use during the operations provided the opportunity to develop individual estimates of average and cumulative exposure. Mortality of the cohort was first compared with that of the Sardinian population. Overall mortality in the cohort was about as expected, but there was a deficit for death from cardiovascular disease and a slight excess for nonmalignant respiratory diseases and lymphatic cancer among the unexposed subcohort. For internal comparisons, we used Poisson regression analysis to calculate relative risks of selected malignant and nonmalignant diseases with the unexposed subcohort as the reference. Cancer mortality was decreased among DDT-exposed workers, mainly due to a reduction in lung cancer deaths. Birth outside from the study area was a strong predictor of mortality from leukemia. Mortality from stomach cancer increased up to 2-fold in the highest quartile of cumulative exposure (relative risk, 2.0; 95% confidence interval, 0.9-4.4), but no exposure-response trend was observed. Risks of liver cancer, pancreatic cancer, and leukemia were not elevated among DDT-exposed workers. No effect of latency on risk estimates was observed over the 45 years of follow-up and within selected time windows. Adjusting risks by possible exposure to chlordane in the second part of the antimalarial operations did not change the results. In conclusion, we found little evidence for a link between occupational exposure to DDT and mortality from any of the cancers previously suggested to be associated. (Cancer Res 2005; 65(20): 9588-94)

Introduction

Dichlorodiphenyltrichloroethane (DDT) has been widely used in the past in antimalarial programs, in the prevention of yellow fever and sleeping sickness, and for agricultural purposes. Although it is recognized as an experimental animal carcinogen by the IARC and many epidemiologic studies of occupational exposure have been conducted, the relationship between DDT and human cancer is still unclear (1). Reports of excess risks of cancers of the lung (2–4), lymphatic and hematopoietic system (5–7), pancreas (8), and liver (9) have been published, but inconsistencies among the studies and limitations in study size, exposure assessment, and study design have precluded definitive conclusions. For example, a pooled analysis of data from three case-control studies on non-Hodgkin's lymphoma conducted in four midwestern states in the United States suggested that exposure to pesticides other than DDT might have confounded the excess risk initially reported (10). A recent follow-up study of DDT applicators in Australia with detailed exposure information (11) found an excess of pancreatic cancer, but only among subjects in the lowest cumulative exposure subgroup. No other excess was observed at any of the other cancer sites explored in this study.

Interest in DDT and cancer research also springs from the wide spectrum of pseudohormonal properties of its isomers and derivatives. *Ortho-para* dichlorodiphenyltrichloroethylene (o,p-DDE) is a xenoestrogen (12), although its ability to attach to the human estrogen receptor in cultured cells is 140 to 300 times weaker than 17β-estradiol, the natural estrogen (13). P-p′-DDE has antiandrogenic properties (14). Inhibition of thyroid function has also been described in relation to DDT (15). Apart from a substantial research effort dedicated to study breast cancer risk associated with internal dose of persistent DDT species, for which the overall evidence is now considered as negative (16, 17), studies of breast cancer by estrogen receptor status, as well as studies of endometrial cancer, prostate cancer, testicular cancer, and thyroid cancer, are quite rare (16, 18).

WHO lists DDT as a persistent organic pollutant to be banned worldwide, although the 2001 Stockholm convention made an important exception for countries where malaria is still endemic. These countries are allowed to keep using the insecticide because of its low cost and effectiveness against malaria vectors. Therefore, sound scientific information on the long-term health effects of DDT use is still needed to allow decision makers in developing countries, where malaria is still one of the leading causes of death, to make the best cost/benefit decisions. The present paper evaluates the mortality among a population of DDT applicators and bystanders who had been exposed to DDT during antimalarial operations in Sardinia, Italy, in 1946 to 1950.

Materials and Methods

DDT was introduced in Sardinia in 1946 to 1950 during an antimalarial campaign supported by the Rockfeller Foundation, the United Nations, and the Italian Government. A pest control agency [Ente Regionale per la Lotta Anti-anofelica in Sardegna (ERLAAS)] was specifically created for the antimalarial operations. Two hundred sixty-seven metric tons of DDT were applied over the whole Sardinian territory (19), corresponding to

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10.6 mg/m^2 or ~190.6 g per resident. Exact figures of the total workforce employed in the antimalarial operations are unknown, and efforts to retrieve the ERLAAS employment registers were not successful. The 1953 report by the ERLAAS director indicated that 32,000, the highest number of employed, was reached in 1948; 24,000 of these were employed in weeding and soil management operations. Based on the number of operative sectors in which the Sardinian territory was divided, each attributed to an individual pesticide applicator, we estimate that ~5,000 workers had direct contact with DDT. The rest of the workforce included subjects employed in inspecting and in support occupations, such as truck drivers and warehouse workers with sporadic and indirect contact with DDT, and laboratory, administrative, and directive staff largely unexposed to the pesticide. As the operations were conducted as separate campaigns, applicators, inspectors, and weeders were hired seasonally, whereas subjects in support occupations, and laboratory, administrative, and directive staff were likely to be more of a stable workforce. It is, therefore, likely that the identified proportion of subjects engaged in the stable, less exposed jobs was larger than the same proportion in exposed jobs. In 1984 to 1986, we reviewed the materials in the ERLAAS archive to assemble a listing of the campaign employees and identified 5,339 subjects from this archive. After excluding 288 duplicates, we extracted personal identification data, job title, and period of employment for 5,051 men employed by the pest control agency in 1946 to 1950 (19).

Retrospective estimate of dichlorodiphenyltrichloroethane exposure. Study subjects were classified as unexposed, directly exposed applicators, and indirectly exposed bystanders (i.e., inspectors, warehouse workers, and truck drivers) based on the occupation at the time of the antimalarial operations. Subjects with multiple occupations involving direct or indirect contact with DDT were assigned to an exposure subgroup based on the occupation with the highest exposure. We used the algorithm developed by Van Hemmen, based on the European Predictive Operator Exposure Model (EUROPOEM) database (20, 21), to estimate DDT daily exposure from inhalation and dermal contact among applicators. The model requires information on state of the product (liquid or powder), method of spraying, dose and spray volume, the representative area sprayed per day, and the application time to provide an estimate of total exposure overall and to fractionate the estimated dose by dermal and inhalation routes. To provide relevant information for the model, we extracted from a report by the last director of the pest control agency (19) the total amount of DDT used, its concentration in the mix used by the applicators (5% or 2.5% water emulsion, or 5% kerosene solution, according to the period), and the prescribed insecticide application for indoor wall surfaces and for outdoors in wetlands. We estimated the amount of DDT that each applicator applied daily, the average size of the houses that were treated, and the number of houses treated daily. Individual exposures were assessed separately for the antifly campaign, which covered the period from October through April, and for the antilarval campaign, which covered the period from May through September each year, and was conducted outdoors by treating wetlands. To estimate exposures during the antilarval phase, we considered average spring-summer weather conditions, the average size of wetlands in the average area treated daily, and DDT concentration in the insecticide mix. To calculate exposure in bystanders, we assumed that it would be similar to that of workers reentering fields after treatment. We recognize that this would not account for differences according to the job, between drivers, warehouse workers, and inspectors. The algorithm to calculate dermal exposure among bystanders was developed by Krebs et al. (22). It calculates dermal exposure in μg/person/d as a function of foliar dislodgeable residue per hectare, number of applications, transfer factor, hours of daily work, application rate, and penetration factor depending on wearing or not protective clothes. Overall, 30 time- and job-specific estimates were elaborated ranging from 54 to 140,400 μg/d. Estimates of DDT daily exposure were then multiplied by the total number of working days and summed to provide a cumulative dose of DDT.

Chlordane exposure was introduced in selected areas for antifly and antilarval purposes. Although it was not possible to distinguish chlordane users from nonusers among applicators, we considered all applicators employed during the periods when chlordane was used as possibly exposed. No quantitative estimates of chlordane exposure were developed because of the lack of measurement data. Exposure to chlordane was not assessed among bystanders.

Vital status and causes of death. Overall, 5,051 male subjects were identified. One hundred thirty-nine women employed exclusively in unexposed jobs were excluded from study. Vital status of study subjects was ascertained from first enrollment in the campaign through December 31, 1999, using the Population Registrar of the last known town of residence. Death certificates for deaths occurring before 1984 were obtained from the same source and from the Registers of the Causes of Death (RENCAM) of the Public Health Department of the Local Health Unit for deaths occurring from 1985 onwards. All the causes of death were reviewed by an expert coder (P. Cocco) and coded using the International Classification of Diseases-9th revision. Date of follow-up was started in January 1, 1956, to allow for a minimum 5-year latency period from the end of exposure, and 104 deaths identified before 1956 were excluded from study. Subjects lost to follow-up were 422 (8.4%), 395 of whom were unidentified and did not enter the follow-up and 27 contributed to person-years up to the last known date of being alive. Therefore, our cohort included 4,552 men, divided in three subcohorts: unexposed (1,291 subjects), applicators (2,578 subjects), and bystanders (683 subjects).

Statistical methods. Each cohort member contributed person-years from January 1, 1956, through December 31, 1999, the date of death, or the date he was lost from follow-up, whichever came first. We first conducted a traditional indirectly standardized mortality study. Age (5-year)– and calendar-year (5-year)–specific rates of the Sardinian male population, available in computerized form for the period from 1971 to 1999, were used for comparison with the mortality experience of the cohort and to calculate indirectly standardized mortality ratios (SMR). Although rates for Sardinia were available for a period shorter than the follow-up, we preferred to restrict the period of follow-up and compare the observed events in the cohort with the expected based on regional Sardinian rates because of important differences in cancer mortality between Sardinia and national Italian rates, particularly for a lower mortality from all cancers, lung cancer, and stomach cancer (23). We used the unexposed subcohort as the internal reference and conducted Poisson regression analysis to model risk of specific causes of death as a function of exposure (cumulative or average exposure and total days of exposure), age at the exit from follow-up (five categories: ≤50, 51-60, 61-70, 71-80, ≥81), age at starting exposure (two categories: ≤30, ≥31), and ethnic origin (whether born in Sardinia or elsewhere). A covariate was also created defining the calendar-year period of work during the antimalarial operations and whether it was a time when only DDT was used or when chlordane was also used. Adjustment for employment during the time when chlordane was used did not appreciably affect risk estimates, so only relative risks (RR) with adjustments for age at exit from follow-up, age at starting exposure, and ethnic origin are presented. Cumulative DDT exposure, total days of exposure, and average daily exposure (cumulative exposure/total days of exposure) were categorized into quartiles for all exposed subjects and within each exposure subgroup.

As no isolated exposure to chlordane was identifiable among this cohort, we explored the effect of chlordane exposure, categorized as ever/never exposed, on risk of mortality from selected causes in applicators only, with reference to the unexposed subgroup by using as the exposure covariate in the regression model a term accounting for the effect of DDT (below or above the median cumulative dose) isolated or with joint chlordane exposure.

Poisson regression analysis was conducted with the AMFIT program, included in the EPICURE software package. The output provides the RR associated with each covariate in the regression model, as the antilogarithm of the respective regression coefficient β. RRs come with the respective 95% confidence intervals (95% CI), calculated according to the Wald formula, as described in the software package:

$$e^{\beta \pm (z_{\alpha/2} * se_\beta)}$$

The statistical significance of trends in relation to cumulative DDT exposure has been calculated, after considering the covariates as

noncategorical, by subtracting from the total deviance of the model not including the covariate of interest, that resulting from the model including it. The value obtained follows a χ^2 distribution with 1 degree of freedom (24).

Results

Table 1 shows the vital status of the cohort. Among the 4,552 subjects 3,037 were deceased and death certificates were retrieved for 89.8% of these (n =2,726). Less than 1% of the cohort was lost to follow-up.

Table 2 shows the distribution of study subjects by job and covariates used in the Poisson regression analysis. Over 40% were applicators, most were born in Sardinia, and mean age at hire was 33.7 years. Only 10% of the individuals worked only with DDT, whereas 70% were potentially exposed to both DDT and chlordane.

The cause-specific SMRs, with reference to the 1971 to 1999 regional mortality rates, are presented in Table 3. Overall mortality in the cohort was similar to that for the general population of Sardinia (SMR = 96.4; 95% CI, 92.7-100.2). It was slightly decreased among the applicators subcohort, mainly due to a strong decrease in cardiovascular mortality (SMR = 68; 95% CI, 62-75). Deaths from cardiovascular diseases were also significantly below the expectation among the unexposed (SMR = 71; 95% CI, 63-82) and bystanders (SMR = 75; 95% CI, 65-86) subcohorts. In the unexposed subcohort, the deficit in cardiovascular mortality was compensated by a parallel increase in nonmalignant respiratory diseases, lung cancer, and lymphatic cancer deaths. Deaths from lung cancer and pancreatic cancer were below expectation among applicators and/or bystanders, whereas stomach cancer mortality was reduced among the unexposed (SMR = 47; 95% CI, 23-97) and bystanders (SMR = 73; 95% CI, 40-131). Due to the incompleteness of the study cohort compared with the estimated total workforce, the SMR findings could be biased if mortality among the unidentified subjects differed from that among identified cohort members. Therefore, we relied primarily upon the Poisson regression analyses, where the unexposed subgroup served as an internal reference.

Table 4 shows the RR for selected causes of death among DDT-exposed subjects and by job subgroups compared with the unexposed workers. No statistically significant excess risk for any cause of death was observed among the all exposed, or among applicators and bystanders, respectively. Total mortality was significantly decreased among the exposed (RR, 0.8) compared with the unexposed. Cancer risk was also reduced among exposed (RR, 0.9; 95% CI, 0.7-1.0), as were deaths from diabetes (RR = 0.5, 95% CI, 0.3-0.9) and cardiovascular diseases (RR = 0.8; 95% CI, 0.7-0.9).

Table 1. Results of the vital status inquiry

Status at the end of follow-up	*n*	%Total
Total subjects entering the cohort	4,552	100.0
Alive	1,492	32.8
Deceased	3,037	66.7
With death certificate	2,726	89.8 (based on total number of deaths)
Cause of death undefined or death certificate not found	311	10.2 (based on total number of deaths)
Lost	23	0.5

Table 2. Distribution of cohort members by job and covariates in the regression analysis

Covariate	*n*	%Total
Job		
Unexposed	1,291	28.4
Applicators	1,974	43.4
Bystanders	1,287	28.2
Origin		
Born in Sardinia	4,250	93.4
Born elsewhere	302	6.6
Pesticide exposure		
DDT only	464	10.2
Worked also in periods when chlordane was also in use	3,218	70.7
Worked only in periods when chlordane was also in use	823	18.1
Undefined dates	47	1.0
Age at commencing exposure		
≤30	2,230	49.0
31+	2,322	51.0
Total	4,552	100.0

Deficits were larger among applicators than bystanders. Risk of stomach cancer was elevated among applicators (RR = 1.6; 95% CI, 0.8-3.3), but not bystanders (RR = 1.1, 95% CI, 0.5-2.4). Mortality from liver cancer, pancreatic cancer, prostate cancer, and leukemia did not differ between the exposed and unexposed subgroups. Only one death from thyroid cancer and no deaths from male breast cancer or testicular cancer occurred in the whole cohort. For nonneoplastic diseases, cardiovascular mortality was reduced 20% among the exposed (RR, 0.8; 95% CI, 0.7-0.9), and it was similar between applicators and bystanders. Mortality from diabetes was also reduced among the exposed, and it did not differ between pesticide applicators and bystanders. Mortality from neurologic diseases and liver cirrhosis did not vary by exposure status. Adjusting the risk estimates for ever having worked during periods when chlordane was also in use did not change the results (not shown in the tables). Seventy-eight deaths occurred among 117 applicators having exposure only to DDT. Of these, 18 (23.1%) were due to cancer (RR, 0.6; 95% CI, 0.3-1.1), including three from stomach cancer (RR, 4.4; 95% CI, 0.7-29.0), four from liver cancer (RR, 1.3; 95% CI, 0.3-4.8), four from pancreatic cancer (RR, 1.5; 95% CI, 0.3-7.3), one from prostate cancer (RR, 0.8; 95% CI, 0.1-15.2), and one from leukemia (RR, 0.8; 95% CI, 0.1-15.2).

Subjects exposed before age 31 had a slightly higher total mortality than those employed at an older age (RR, 1.1; 95% CI, 1.0-1.2), whereas cancer mortality (RR, 0.8; 95% CI, 0.6-0.9), and particularly lung cancer (RR, 0.5; 95% CI, 0.4-0.8), were significantly decreased among these subjects. Subjects born elsewhere had an increased risk of mortality from stomach cancer (RR, 2.0; 95% CI, 0.7-5.7), prostate cancer (RR, 1.8; 95% CI, 0.6-5.2), and leukemia (RR, 5.7; 95% CI, 2.0-16.3) compared with those born in Sardinia (data not shown).

Mortality was also explored in relation to estimated level of exposure (Table 5A and B). No significant increasing trends in risk were observed by quartiles of cumulative exposure (Table 5A) or average daily exposure (Table 5B) to DDT for any cancer site. Risk of stomach cancer, however, increased with cumulative DDT exposure (and was of borderline statistical significance: χ^2 for

Table 3. Standardized mortality rates in the total cohort and subcohorts in reference to the regional mortality rates in 1971 to 1999

	Total cohort (Pyr: 83,748.33)			Unexposed (Pyr: 21,727.82)			Bystanders (Pyr: 25,321.77)			Applicators (Pyr: 36,698.74)		
	O/E	SMR	95% CI	O/E	SMR	95% CI	O/E	SMR	95% CI	O/E	SMR	95% CI
All deaths	2,543/2,638.0	96	93-100	699/695.0	101	93-108	689/680.1	101	94-109	1,155/1,262.8	91	86-97
All cancers	707/671.3	105	98-113	699/695.0	101	93-108	218/188.6	116	101-132	02/310.2	97	87-109
Stomach cancer	43/57.2	75	56-101	7/14.82	47	23-97	11/15.1	73	40-131	25/27.2	92	62-136
Liver cancer	58/57.3	101	78-131	14/14.8	94	56-160	18/16.2	111	70-177	26/26.4	99	67-145
Pancreatic cancer	28/32.9	85	59-123	7/8.5	83	39-173	9/9.2	98	51-188	12/15.2	79	45-139
Lung cancer	191/185.3	103	89-119	56/47.5	118	91-153	67/55.0	122	96-155	68/82.8	82	65-104
Prostate cancer	44/56.0	79	58-105	14/14.2	99	58-167	58/57.3	101	78-131	21/27.7	101	50-116
Bladder cancer	37/40.2	92	67-127	8/10.2	101	39-156	8/11.1	72	36-144	21/19.0	111	72-170
Lymphatic cancer	49/42.8	115	87-151	19/10.9	174	112-271	10/12.1	83	44-153	20/19.8	101	65-157
Leukemia	24/22.5	107	72-159	8/5.7	140	70-278	6/6.3	96	43-213	10/10.5	95	51-177
Neurologic diseases	30/32.9	91	64-130	8/8.4	95	48-190	11/9.1	121	67-219	11/15.4	71	40-128
Diabetes	54/60.9	89	68-116	18/15.5	116	73-185	16/16.2	99	61-161	20/29.3	68	44-105
Cardiovascular diseases	792/1,121.4	71	66-76	214/299.5	71	63-82	204/273.3	75	65-86	374/548.6	68	62-75
NMRD	266/266.8	100	88-112	88/69.2	127	103-157	60/67.2	89	69-115	118/130.5	90	76-108
Liver cirrhosis	65/114.2	60	45-72	15/29.5	51	31-84	20/32.6	61	40-95	30/52.0	58	40-82

Abbreviations: NMRD, nonmalignant respiratory diseases; Pyr, person-years; O/E, observed/expected deaths.

trend = 3.72; $0.05 > P < 0.10$) and showed increased RRs in each category of average exposure (although they did not show a monotonic increase). When trends were explored by quartiles of average daily exposure among applicators only, no significant increasing trend was observed (not shown in the tables). Significantly inverse trends by total days of exposure were observed for all cancers (test for trend = 13.69, $P < 0.01$) and lung cancer (test for trend = 11.24, $P < 0.01$). A significant inverse tend by total days of exposure was also observed for prostate cancer (test for trend = 4.28, $P < 0.05$).

Effect of latency (years since first exposure) on cancer risks was explored for selected cancers among DDT applicators. Risk of stomach cancer, liver cancer, pancreas cancer, prostate cancer, and leukemia were calculated allowing for 10, 15, 20, 25, and 30 years from the end of the antimalarial operations. No significant variations in risk for any of the explored cancer sites by years since last exposure. The small excess risk of stomach cancer did not vary by latency. Risk for the same cancer sites was explored within specific windows of follow-up. No changes in risk were observed (not shown in the tables).

Table 4. Cause-specific mortality risk in 1956 to 1999 by DDT exposure category as defined by job, adjusted by age at exit for follow-up, age at first exposure, and ethnicity, with reference to the unexposed subcohort

	Unexposed (Pyr: 40,187.88)		All exposed (Pyr: 113,340.16)		Bystanders (Pyr: 44,957.71)		Applicators (Pyr: 68,382.45)	
	n	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)
All deaths	888	1.0 (—)	2,149	0.8 (0.7-0.9)	807	0.8 (0.8-0.9)	1,342	0.8 (0.7-0.8)
All cancers	228	1.0 (—)	573	0.9 (0.8-1.0)	240	1.0 (0.8-1.2)	333	0.8 (0.7-1.0)
Stomach cancer	11	1.0 (—)	45	1.4 (0.7-2.7)	13	1.1 (0.5-2.4)	32	1.6 (0.8-3.3)
Liver cancer	21	1.0 (—)	51	0.9 (0.5-1.4)	20	0.9 (0.5-1.7)	31	0.8 (0.4-1.4)
Pancreas cancer	9	1.0 (—)	22	0.8 (0.4-1.8)	9	0.9 (0.3-2.2)	13	0.8 (0.3-1.9)
Lung cancer	68	1.0 (—)	150	0.8 (0.6-1.1)	78	1.1 (0.8-1.5)	72	0.6 (0.4-0.8)
Prostate cancer	24	1.0 (—)	47	0.7 (0.4-1.1)	14	0.6 (0.3-1.2)	33	0.7 (0.4-1.2)
Bladder cancer	11	1.0 (—)	34	1.0 (0.5-2.1)	11	1.0 (0.4-2.3)	23	1.0 (0.5-2.1)
Lymphatic cancer	20	1.0 (—)	35	0.7 (0.4-1.1)	12	0.6 (0.3-1.2)	23	0.7 (0.4-1.3)
Leukemia	8	1.0 (—)	18	0.9 (0.4-2.2)	6	0.8 (0.3-2.3)	12	1.1 (0.4-2.8)
Neurologic diseases	8	1.0 (—)	22	0.8 (0.3-1.7)	10	1.0 (0.4-2.6)	12	0.6 (0.2-1.4)
Diabetes	22	1.0 (—)	33	0.5 (0.3-0.9)	14	0.6 (0.3-1.2)	19	0.5 (0.3-1.9)
Cardiovascular diseases	258	1.0 (—)	632	0.8 (0.7-0.9)	229	0.8 (0.7-1.0)	403	0.8 (0.7-0.9)
NMRD	88	1.0 (—)	95	0.7 (0.5-0.9)	60	0.8 (0.6-1.1)	35	0.5 (0.4-0.8)
Liver cirrhosis	21	1.0 (—)	59	1.0 (0.6-1.6)	25	1.1 (0.6-1.9)	34	0.9 (0.5-1.6)

Table 5. Mortality follow-up (1956-1999) among DDT-exposed workers: relative risks by quartile of cumulative and average exposure

A. Cumulative exposure quartiles

	Unexposed (Pyr: 40,172.96)		0.01-21.6 mg (Pyr: 27,787.44)		21.7-531.4 mg (Pyr: 27,313.08)		531.5-2,755 mg (Pyr: 28,017.29)		≥2,755.1 mg (Pyr: 27,366.03)		χ^2 test for trend (*P*)
	n	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	
All deaths	888	1.0 (—)	510	1.0 (0.9-1.1)	544	1.0 (0.9-1.1)	550	0.9 (0.8-1.0)	545	0.8 (0.7-0.9)	13.07 (<0.001)
All cancers	228	1.0 (—)	154	1.1 (0.9-1.4)	133	0.9 (0.7-1.1)	134	0.9 (0.7-1.1)	152	1.0 (0.8-1.2)	1.38 (NS)
Stomach cancer	11	1.0 (—)	8	1.2 (0.5-3.0)	8	1.1 (0.5-2.8)	13	1.7 (0.7-3.7)	16	2.0 (0.9-4.4)	3.72 (0.05 > *P*< 0.10)
Liver cancer	21	1.0 (—)	13	1.0 (0.5-2.1)	16	1.2 (0.6-2.4)	8	0.5 (0.2-1.2)	14	1.0 (0.5-1.9)	0.50 (NS)
Pancreas cancer	9	1.0 (—)	6	1.1 (0.4-3.1)	8	1.4 (0.5-3.6)	5	0.8 (0.3-2.5)	3	0.5 (0.1-1.8)	0.87 (NS)
Lung cancer	68	1.0 (—)	55	1.3 (0.9-1.8)	32	0.7 (0.5-1.1)	29	0.6 (0.4-1.0)	34	0.7 (0.5-1.1)	6.73 (<0.01)
Prostate cancer	16	1.0 (—)	6	0.6 (0.3-1.7)	8	0.8 (0.3-1.9)	7	0.6 (0.3-1.5)	10	0.9 (0.4-1.9)	0.27 (NS)
Bladder cancer	11	1.0 (—)	5	0.8 0.3-2.3	6	0.9 (0.3-2.3)	11	1.4 (0.6-3.3)	12	1.5 (0.7-3.4)	1.67 (NS)
Leukemia	8	1.0 (—)	5	1.1 (0.4-3.5)	3	0.7 (0.2-2.8)	6	1.3 (0.5-3.9)	4	0.8 (0.2-2.9)	0.03 (NS)

B. Average exposure quartiles

	Unexposed (Pyr: 41,072.96)		0.001-0.061 mg (Pyr: 28,145.26)		0.062-6.533 mg (Pyr: 31,361.09)		6.534-9.868 mg (Pyr: 24,106.32)		≥9.869 mg (Pyr: 26,871.16)		χ^2 test for trend (*P*)
	n	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	
All deaths	888	1.0 (—)	521	1.0 (0.9-1.1)	587	0.9 (0.8-1.0)	480	0.9 (0.8-1.0)	561	0.9 (0.8-1.0)	9.69 (<0.005)
All cancers	228	1.0 (—)	160	1.1 (0.9-1.4)	151	0.9 (0.7-1.1)	126	1.0 (0.8-1.2)	136	0.9 (0.7-1.1)	2.89 (NS)
Stomach cancer	11	1.0 (—)	8	1.2 (0.5-3.0)	11	1.4 (0.6-3.2)	14	2.1 (0.9-4.6)	12	1.5 (0.7-3.4)	2.09 (NS)
Liver cancer	21	1.0 (—)	15	1.2 (0.6-2.3)	12	0.8 (0.4-1.6)	7	0.5 (0.2-1.3)	17	1.2 (0.6-2.2)	0.09 (NS)
Pancreas cancer	9	1.0 (—)	5	0.9 (0.3-2.7)	8	1.2 (0.5-3.2)	4	0.8 (0.2-2.6)	5	0.8 (0.3-2.5)	0.10 (NS)
Lung cancer	68	1.0 (—)	50	1.1 (0.8-1.7)	41	0.8 (0.6-1.2)	28	0.7 (0.5-1.1)	31	0.7 (0.4-1.1)	5.70 (<0.05)
Prostate cancer	16	1.0 (—)	6	0.6 (0.2-1.6)	9	0.8 (0.4-1.8)	9	1.0 (0.4-2.2)	7	0.6 (0.2-1.5)	0.61 (NS)
Bladder cancer	11	1.0 (—)	6	0.9 (0.3-2.5)	8	1.0 (0.4-2.5)	11	1.6 (0.7-3.8)	9	1.1 (0.5-2.7)	0.52 (NS)
Leukemia	8	1.0 (—)	5	1.2 (0.4-3.6)	6	1.3 (0.4-3.7)	3	0.8 (0.2-2.9)	4	0.8 (0.2-2.9)	0.15 (NS)

NOTE: As in Tables 3 and 4, risks are adjusted by age, age at first exposure, and ethnic origin.

Discussion

In our follow-up study, occupational exposure to DDT and chlordane did not show any clear excess for any cause of death. Stomach cancer was slightly elevated and tended to increase with estimated cumulative exposure. There was, however, a significant deficit in mortality among exposed cohort members for total mortality, diabetes, and cardiovascular disease. Lung cancer was also significantly reduced among applicators. These deficits could be due to differences in tobacco use among exposed and unexposed cohort members. Unfortunately, we lacked information on tobacco. As an indirect assessment of differences in smoking habits by job in our cohort, we calculated the RR for nonmalignant respiratory disease in applicators and bystanders with reference to the unexposed subcohort. DDT applicators showed a significant decrease in nonmalignant respiratory disease risk (RR, 0.5; 95% CI, 0.4-0.8), whereas risk was nonsignificantly decreased among bystanders (RR, 0.8; 95% CI, 0.6-1.1). Risk of smoking-related cancers other than lung cancer, as defined by the IARC in 1986 (namely, cancers of the oral cavity, pharynx, larynx, esophagus, pancreas, bladder, and kidney; ref. 25) and 2002 (same as in 1986 plus some other pathologic types of esophageal and renal cancer, nasal cancer, stomach cancer, liver cancer, and myeloid leukemia; ref. 26), was also calculated by job. Again, among applicators, risk for the 1986 list of smoking-related cancers other than lung cancer was significantly decreased (RR, 0.5; 95% CI, 0.3, 1.0), whereas risk for the 2002 IARC list of smoking related cancers was not (RR, 0.8; 95% CI, 0.5, 1.1). No such decrease in risk for smoking-related cancers other than the lung was observed among bystanders. These findings suggest that differences in smoking might contribute to the lower mortality for tobacco-related causes of death observed among applicators. As previously acknowledged, no direct information is available on smoking habits of this cohort. However, film documentaries and internal publications by the pest control agency indicate that applicators were unskilled workers temporarily hired village by village and trained according to the need. Skilled workers, such as drivers and mechanics, and other more educated workers, such as clerks, lab people, warehouse workers, and foremen, were hired permanently and more frequently were of non-Sardinian origin (11.7% among unexposed, 7.6% among bystanders, and 2.7% among applicators). The extreme poverty of local unskilled workers in the postwar years might have made more difficult for them to have access to tobacco products than subjects with a permanent job.

Birth elsewhere than Sardinia was a strong predictor of mortality from leukemia. There is no clear explanation for this finding, although it is another example where cancer mortality in the Sardinian population differs from the national figures.

Mortality from stomach cancer showed a significant 2-fold excess among DDT-exposed workers in the highest quartile of cumulative exposure. Although risks tended to increase with cumulative and average exposure, the trend was not significant. Also, no effect of latency was observed, as risk remained steady over the 45 years of follow-up and within selected time windows. Low social class and unhealthy dietary habits are the main risk factors for stomach cancer, with occupational factors playing a minor role, if any (27). Farmers have been considered at risk, and a role of pesticide exposure has been postulated (27–29). However, no specific agricultural exposure has been identified and the rural association may have resulted from confounding by lifestyle habits associated with rural residence (29). We adjusted for ethnicity to partially control for differences in education and dietary habits between the unexposed, who more frequently were from non-Sardinian origin, and the exposed subcohorts. Differences in hygienic conditions of housing and diet between permanent skilled workers and temporary unskilled applicators might have generated the observed moderated excess in stomach cancer deaths among applicators.

Pancreatic cancer mortality was not elevated in our study, but as the observed deaths were very few we cannot exclude a positive association. A link with pancreatic cancer risk was suggested by Garabrant et al. (8), but inconsistent findings were recently reported in an Australian cohort, with a significant excess associated with the lowest exposure level (11), and in an U.S. case-control study by serum DDE level (30). Reasons for pancreas to be a target of human DDT carcinogenicity are unclear, although DDT and its metabolites have been suggested to play a role in the pathogenesis of exocrine pancreatic cancer through modulation of K-*ras* activation (31). The IARC considers cigarette smoking as an important cause of pancreatic cancer (25).

Reports of an association between cancer of the liver (9, 32), lung (2–4), and lymphatic and hematopoietic system (5–7) and DDT exposure were not confirmed in our study. We saw a slight deficit of prostate cancer among the exposed individuals. The literature on prostate cancer and DDT is conflicting. This effect has been hypothesized because of the anti-androgenic activity of p,p′-DDE, the main DDT metabolite. Excesses of prostate cancer have been observed among farmers, who may have had contact with DDT (28). A significant 37% excess risk for prostate cancer, but no evidence of a dose-response trend, has been reported among farmers exposed to DDT in the U.S. Agricultural Health Study (33). However, no association was observed in a geographic correlation study (34). Associations were also explored with chlordane exposure, as well as its interaction with DDT exposure. We saw differences in RR between those exposed to DDT alone or to DDT plus chlordane. However, interpretation is uncertain because of small numbers and the lack of precision in the definition of chlordane exposure.

A major strength in our study is the availability of exposure information that could be used to construct an approximate estimate of individual exposure. Previous studies used surrogates, such as days of exposure (11), or work records (2), or self-reported questionnaire information (5–7, 10) to derive qualitative indicators of DDT exposure. The U.S. Agricultural Health Study was the first to include a detailed exposure assessment (35), although estimates were based on scores and were, therefore, not comparable with our quantitative exposure estimates. Our study also had a unique pattern of pesticide exposure, which included only two pesticides, namely DDT and chlordane, with some possibility of disentangling the respective effects. The study cohort, however, is incomplete (we identified only 4,552 of ~8,000 campaign workers) and this could introduce a bias if unidentified individuals differed in exposure and/or disease outcome from the identified cohort members. With the purpose of minimizing the chances of inclusion bias, we used the unexposed subcohort as the internal reference in our study. This approach would not, however, be effective if the exclusion was differential, and the DDT applicators tended to be more likely to be excluded because of death at earlier age than the less exposed or unexposed. Unfortunately, it was not possible to assess the missing workforce by job. We were able to identify 91.6% of the subjects in the agency archive, which we consider acceptable in relation to the distance in time from assembling the cohort, and we determined the vital status for 99.5% of the subjects entering the cohort. The search of death certificates was less successful, and overall they could be found for 89.8% of the deceased subjects. A reason could be the long time period covered by follow-up, with a greater proportion of losses in the early years. In fact, the proportion of death certificates not found was 18.5% in the first 10 years of follow-up (1956-1965); it decreased to 13.4% in the second decade (1966-1975); and it remained stable ranging between 8.4% and 8.6% in 1976 to 1985, 1986 to 1995, and 1996 to 1999. Also, the loss was similar between applicators (171/1,155 total deaths, 14.8%) and the unexposed subcohort (104/699 total deaths, 14.9%), whereas the proportion was smaller among bystanders (36/689, 5.2%). As the unexposed subcohort was the internal reference population, we reasonably assume that incompleteness in death certificate availability did not significantly affect the risk estimates.

The occupational exposure to DDT in this cohort being concentrated in a relatively short period may not have led to large enough differences in individual cumulative exposure to show effects. We estimated individual exposures based on the concentration of DDT in the pesticide mix and whether outdoor or indoor spray was done. The number of work days associated with each of the 30 time- and job-specific exposure estimates was a further factor differentiating individual cumulative exposures, which ranged from 0.000054 to 32.4 g. We considered such a range large enough to make evident dose-related effects, if present. Finally, the long half-life of DDT and its derivatives in the living organisms (36) extends the relevant time of the internal exposure well beyond the relatively short periods in which the high doses were accumulated from external sources. Lack of information on lifestyle factors and smoking also complicates interpretation of our data.

In conclusion, we did not find a link between occupational DDT exposure and mortality from any of the cancers previously associated with exposure to this chemical. Numbers for some causes, however, were relatively small, which limited the opportunity to identify smaller risks. Mortality deficits observed might be due to residual inclusion bias and differences in tobacco use.

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